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VATERL: An Epidemiologic Analysis of Risk Factors

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This work analyzed the incidence of risk factors in 138 cases presenting two or more of five components defining VATERL, with no other recognized unrelated anomalies: vertebral anomalies, anal atresia, esophageal atresia with or without tracheoesophageal fistula, renal anomalies, and preaxial defects of the upper limbs, including polydactyly of the thumb. The 138 infants were ascertained among 1,811,461 births examined in the 1967–1994 period by the Latin-American Collaborative Study of Congenital Malformations: ECLAMC. One healthy and one malformed control newborn infant were matched to each VATERL case.

The birth prevalence rates (per 100,000 births) for VATERL were significantly lower in Venezuela (3.1) than in the other eight countries (8.8) ($P < 0.001$). Venezuela also had lower rates for all five VATERL defects, even after excluding the 138 VATERL cases.

VATERL cases were preferentially males (male proportion 0.6261) ($P < 0.02$), and, when compared with healthy controls, they had a higher perinatal mortality rate (63.7%) ($P < 0.005$), a higher frequency of fetal losses in previous pregnancies (12.6%) ($P < 0.05$), and lower mean birthweights (2,361.79 ± 809.63 g) ($P < 0.005$).

VATERL cases showed a higher rate than matched malformed controls for prenatal exposures to drugs and physical agents ($P < 0.02$ and $P < 0.05$, respectively), although no specific pharmacological or physical group was involved.

The lower birth prevalence rates found in Venezuela, for VATERL as well as for each of the five congenital anomalies involved in this association, seem to be biologically meaningful. Since we could not identify a potential risk factor, nor a common cause of underascertainment unique to the Venezuelan subsample and common to all six hospitals, no hypothesis can be advanced here for this phenomenon. Nevertheless, this unequal geographic distribution strongly suggests a common etiopathogenicity for the five congenital anomalies involved in the VATERL association. Am. J. Med. Genet. 73:162–169, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: VATERL; risk factors; congenital anomalies

INTRODUCTION

In an attempt to attain a nosological understanding of the VATERL association, the authors first defined and delineated this combination of birth defects as the coexistence of five "unrelated" anomalies, namely vertebral anomalies, anal atresia, esophageal atresia with or without tracheoesophageal fistula, renal anomalies, and preaxial limb deficiency [Rittler et al., 1996]. As a second step, we evaluated the incidence of risk factors in those VATERL patients, in order to detect clues concerning the cause and pathogenesis of this common, well-recognized but still intriguing dysmorphogenetic entity.

MATERIALS AND METHODS

This study was based on data collected by the Latin-American Collaborative Study of Congenital Malformations (ECLAMC). ECLAMC is a case-control, hospital-based, study of congenital anomalies, operating since 1967 with births reported from more than 100 participating maternity hospitals distributed over several South American countries [Castilla and Orioli, 1983].

The material for this study includes 1,811,461 newborn infants born in the ECLAMC hospital network during the 1967–1994 period. All consecutive livebirths

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and stillbirths with a birthweight of 500 g or more were examined by a trained pediatrician, according to a preestablished protocol.

The following criteria were used to define VATERL cases: two or more of any of the five components recognized as part of the VATERL association, namely, vertebral anomalies, anal atresia, esophageal atresia with or without tracheoesophageal fistula, renal anomalies, and preaxial defects of the upper limbs, including polydactyly of the thumb. Anomalies pathogenically related to the VATERL components, or because of their high association rate with VATERL, were accepted as "expanded" VATERL cases, namely, other intestinal or respiratory anomalies, single umbilical artery, genital and cardiovascular anomalies. Further details of these definitions were published [Rittler et al., 1996].

One healthy and one malformed control infant was taken for each VATERL case. The next nonmalformed baby of the same sex, born in the same hospital, was selected as the healthy control subject for each case, while the next baby of the same sex, affected by a major defect, which could include isolated VATERL components, and born in the same hospital was selected as the "sick" control. Collaborating physicians collected information on each registered case or control infant and their mothers, using protocols specifically designed for this purpose [Castilla and Lopez-Camelo, 1990].

A total of 7,794 infants with two or more congenital anomalies were registered in this database (43.03/10,000), and 138 (0.76/10,000) of these fit our working definition of the VATERL association, presenting no other major malformations. The birth prevalence distribution of the five VATERL component defects was also analyzed after excluding those cases involved in the VATERL association. Recognized syndromes were not excluded. There were 216 cases with vertebral anomalies, 533 cases with anal atresia, 309 cases with esophageal atresia, 643 cases with renal anomalies, and 502 cases with radial defects.

Time series of birth prevalence rates were taken by 3-year intervals for secular trends, and by month of birth for seasonal distribution. Chi-square test for linear trend was used for the former, while the usual parametric [Walter and Elwood, 1975] and nonparametric [Hewitt et al., 1971] tests were used for the latter. Country of birth was used for the geographical distribution, taking ECLAMC samples of nine South American countries, Paraguay and the three Guyanas excluded.

Sex proportions were compared with those of the examined birth population (0.5111). For the following variables, with no expected recall bias, VATERL cases were compared with their matched healthy controls: perinatal mortality (stillbirth plus livebirth with early neonatal death); twinning; birthweight; gestational length (age of amenorrhea); primiparity; maternal and paternal age; maternal and paternal educational levels; maternal and paternal occupational levels; parental consanguinity; ethnicity. Native (defined as Amerindian plus Latin-European) and Black ancestry were taken as indicators for ethnicity.

Parental fertility was approached in three different ways: a direct question concerning maternal difficulties in becoming pregnant and being considered as positive only if studies or treatments were required; the frequency of fetal losses (miscarriages plus stillbirths) in previous pregnancies; and the frequency of an adverse pregnancy outcome (miscarriage, stillbirth, or malformation) in the mother's immediate previous pregnancy.

For those risk factors subjected to maternal recall bias, VATERL cases were compared with their matched malformed controls. They were relatives affected with any congenital anomaly and prenatal exposure, during the first trimester of pregnancy, to drugs, vaccinations, physical factors, acute and chronic maternal illness, and vaginal bleeding.

Intrauterine growth was analyzed by subtracting the birthweight of VATERL cases from that corresponding to the 10th centile of nonmalformed newborn infants of the same gestational age. When the difference was negative, the case was considered as having intrauterine growth retardation (IUGR). Thus, it was expected that no more than 10% of the cases would present IUGR. This reference material corresponds to 37,094 controls, matched one-to-one to all the malformed infants diagnosed in the 1967–1994 period, where birthweight and gestational age were specified and after removal of cases with extreme values, namely, below 500 g and above 7,000 g for weight, and below 140 and above 302 days for length of gestation. Expected values of birthweight for each week interval of gestational age were smoothed by a fifth degree polynomial.

RESULTS

Time Series

There was a significantly increasing secular trend in the birth prevalence rates for VATERL cases, mainly since 1986. Similarly increasing secular trends were also observed for three of the five VATERL component anomalies in non-VATERL cases, namely vertebral anomalies (V), anal atresia (A), and renal defects (R) (Table I).

No differences in seasonal distribution were observed, according to the date of birth of VATERL cases. Walter and Elwood [1975]: $\chi^2 = 0.36$; df: 2; theta: 23.31; month: July; $P > 0.05$; Hewitt et al. [1971]: RS: 54; period: July–December; $P > 0.05$.

Geographic Distribution

The birth prevalence rates for isolated VATERL cases (with no other recognized unrelated anomalies) were heterogeneous among the nine collaborating countries ($\chi^2 = 20.69$; df: 8; $P = 0.00425$), mainly due to a significantly lower rate in Venezuela (3.1/100,000 births) than in the other eight countries (8.8/100,000) ($\chi^2 = 11.94$; df: 2; $P < 0.001$) (Table II). In order to establish if this finding could be explained by a previously recognized low rate of tracheoesophageal fistula (TE) in Venezuela [Robert et al., 1993], the distributions by country of birth were also analyzed independently for TE and for VATERL. Venezuela had significantly lower birth prevalence rates than the remaining eight countries for three of the four tested diagnostic

TABLE I. Secular Distribution of VATERL Association and VATERL Components by 3-Year Intervals*

	VATERL		V		A		TE		R		L		Births
Years	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N
1967–1970	9	6.4	10	7.1	37	26.3	14	9.9	18	12.8	36	25.6	140,713
1971–1973	7	4.3	16	9.8	43	26.4	22	13.5	16	9.8	34	20.9	162,951
1974–1976	9	3.9	9	3.9	48	21.0	37	16.2	31	13.6	61	26.7	228,167
1977–1979	8	3.8	22	10.5	63	30.0	42	20.0	32	15.2	69	32.9	209,888
1980–1982	8	5.0	19	11.8	52	32.2	27	16.7	38	23.6	35	21.7	161,252
1983–1985	6	4.5	19	14.2	41	30.6	23	17.1	42	31.3	54	40.3	134,117
1986–1988	20	14.5	29	21.1	43	31.2	33	24.0	69	50.0	42	30.5	137,759
1989–1991	21	11.0	25	13.1	71	37.3	32	16.8	98	51.5	57	30.0	190,229
1992–1994	50	11.2	67	15.0	135	30.2	79	17.7	299	67.0	114	25.5	446,385
Total	138	7.6	216	11.9	533	29.4	309	17.1	643	35.5	502	27.7	1,811,461
χ^2 =	20.36		16.99		4.54		3.02		240.44		0.37		
P =	0.00001		0.00004		0.03		0.082		0.00001		0.54		

*Rates per 100,000 births. χ^2 for linear trend; df: 8.

categories involving TE: TE (χ^2 = 41.05; df: 2; P < 0001), VATERL with TE (χ^2 = 8.36; df: 2; P < 0.005) (Table III), and TE without VATERL (χ^2 = 32.01; df: 2; P < 0.0001) (Table IV). VATERL without TE, with only nine cases observed in Venezuela did not reach statistical significance (χ^2 = 3.70; df: 2; P > 0.05).

When countries were compared for the birth prevalence rates of the five VATERL components, after excluding the 138 VATERL cases, Venezuela had lower values than the remaining eight countries for all of the five defects (Table IV).

In order to test the hypothesis of a generalized underascertainment of birth defects in the six Venezuelan hospitals, the birth prevalence rate for Down syndrome was compared, after adjustment for maternal age, between Venezuela (487/381,285 = 0.00128, adjusted: 0.00143) and the rest of the South American sample (2,111/1,430,176 = 0.00148, adjusted: 0.00146). The observed values were similar in both groups (χ^2 = 0.44; df: 2; P = 0.507).

Since the observed geographic differences could be just spurious or due to arbitrary boundaries, comparisons were also made between eastern (three hospitals) and western (three hospitals) Venezuela and Colombia, the only neighboring country to Venezuela in our sample, as the Brazilian northern region is not included in the ECLAMC birth series. Furthermore, Brazil, representing one half of the South American population cannot be considered as a single geographic unit in this context.

The birth prevalence rates for cases with any of the five VATERL component anomalies (excluding VATERL cases) were similar in eastern (126/196,216 = 64.2/100,000) and western (115/185,069 = 62.1/100,000) Venezuela (χ^2 = 0.04; df: 1; P > 0.05); significantly lower in Venezuela (241/381,285 = 63.2/100,000) than in Colombia (35/31,852 = 109.9/100,000) (χ^2 = 8.91; df: 1; P < 0.005), as well as in the remaining seven countries (1,927/1,398,324 = 137.8/100,000) (χ^2 = 136.42; df: 1; P < 0.00001); and were similar in Colombia (35/31,852 = 109.9/100,000) as in the remaining seven countries (χ^2 = 1.57; df: 1; P > 0.05) (Table IV; Fig. 1).

Sex, Mortality, Birthweight

VATERL cases were preferentially males (male proportion 72/115 = 0.6261; 23 cases with ambiguous genitalia and no other sex evidence available were ex-

TABLE II. Geographic Distribution of VATERL Cases*

	Births	VATERL cases	
Country	N	N	Rates
Argentina	713,028	71	10.0
Bolivia	47,733	4	8.4
Brazil	270,224	28	10.4
Chile	186,820	13	7.0
Colombia	31,852	1	3.1
Ecuador	70,918	2	2.8
Peru	21,504	0	0.0
Uruguay	88,097	7	7.9
Venezuela			
East	196,216	7	3.6
West	185,069	5	2.7
Total	381,285	12	3.1
Total	1,811,461	138	7.6

*Rates per 100,000 births.

TABLE III. Geographic Distribution of Esophageal Atresia (TE), TE in VATERL Cases, and VATERL Cases Without TE (for Non-VATERL Cases With TE See Table IV)*

			VATERL			
	TE		With TE		Without TE	
Country	N	Rate	N	Rate	N	Rate
Argentina	176	24.7	33	4.6	38	5.3
Bolivia	15	31.4	2	4.2	2	4.2
Brazil	67	24.8	12	4.4	16	5.9
Chile	47	25.2	5	2.7	8	4.3
Colombia	2	6.3	0	0.0	1	3.1
Ecuador	15	21.2	2	2.8	0	0.0
Peru	6	27.9	0	0.0	0	0.0
Uruguay	14	15.9	3	3.4	4	4.5
Venezuela						
East	15	7.6	2	1.0	5	2.5
West	12	6.5	1	0.5	4	2.2
Total	27	7.1	3	0.8	9	2.4
Total	369	20.4	60	3.3	78	4.3

*Rates per 100,000 births.

TABLE IV. Geographic Distribution of VATERL Components After Excluding 138 VATERL Cases*

	V		A		TE		R		L		Totals	
Country	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Argentina	117	16.4	226	31.7	143	20.1	217	30.4	221	31.0	924	129.6
Bolivia	0	0.0	39	81.7	13	27.2	3	6.3	21	4.4	76	159.2
Brazil	42	15.5	67	24.8	55	20.4	225	83.3	67	24.8	456	168.7
Chile	21	11.2	60	32.1	42	22.5	102	54.6	65	34.8	290	155.2
Colombia	4	12.6	9	28.3	2	6.3	9	28.3	11	34.5	35	109.9
Ecuador	4	5.6	25	35.3	13	18.3	5	7.1	30	42.3	77	108.6
Peru	2	9.3	7	32.6	6	27.9	1	4.7	6	27.9	22	102.3
Uruguay	9	10.2	31	35.2	11	12.5	15	17.0	16	18.2	82	93.1
Venezuela												
East	8	4.1	34	17.3	13	6.6	32	16.3	39	19.9	126	64.2
West	9	4.9	35	18.9	11	5.9	34	18.4	26	14.0	115	62.1
Total	17	4.5	69	18.1	24	6.3	66	17.3	65	17.1	241	63.2
Total	216	11.9	533	29.4	309	17.1	643	35.5	502	27.7	2,203	121.6
χ^2 df = 8		41.28		66.57		42.27		276.03		36.09		191.10
$P <$		0.0001		0.0001		0.0001		0.0001		0.0001		0.0001
χ^2 df: 2 =		22.58		20.58		32.00		44.37		18.34		135.02
$P <$		0.0001		0.0001		0.0001		0.0001		0.0001		0.0001

*Rates per 100,000 births. χ^2 df:8 homogeneity among nine countries (only total of Venezuela considered). χ^2 df:2 Venezuela vs. other countries.

cluded) as compared with the total birth population (male proportion = 0.5111) ($P < 0.02$).

When compared with matched healthy controls, VATERL cases presented a significantly higher perinatal mortality rate (63.7%) ($P < 0.005$), a higher frequency of fetal losses in previous pregnancies (12.6%) ($P < 0.05$), and lower mean birthweights (2,361.79 ± 809.63 g) ($P < 0.005$) (Table V).

The high perinatal mortality rate (63.7%) was largely due to early neonatal deaths (49.6%), while fetal deaths were less frequent (14.1%).

Mean gestational ages were 37.7 ± 4.4 weeks in VATERL cases and 39.5 ± 2.2 in controls ($P < 0.005$) (Table V). The observed number of cases with IUGR (birthweight below the 10th centile for gestational age) was significantly higher when compared with the expected value ($\chi^2 = 23.45$; df:1; $P < 0.000001$).

No significant differences were observed between cases and controls for twinning, parental ages, primigravidity, parental consanguinity, Black or Native racial ancestry, parental education, parental occupation, difficulties to conceive, and adverse reproductive outcome in the immediate previous pregnancy.

VATERL cases were grouped into two categories of gestational age, one with 35 or more weeks (67 cases) and another with less than 35 weeks (28 cases; 43 with unspecified data). The available variables were compared between both groups, and a significant difference was only observed for early neonatal deaths, which were more frequent in the group under 35 weeks, while stillbirths were not.

Prenatal Exposures

The prenatal variables, as compared with sex-matched malformed controls, showed a significantly higher rate for prenatal exposure to drugs and physical agents ($P < 0.02$ and $P < 0.05$, respectively) (Table V).

Of 138 mothers of VATERL patients, 54 had taken one or more drugs during the first trimester of pregnancy (42.5%), while the corresponding number for controls was 37 mothers (27.6%). The most frequently used drug groups were (number of cases/controls in parentheses): 1) sex hormones (9/6); 2) antibiotics (9/0), including three unspecified; five penicillin or its derivatives and one tetracycline; 3) antianemic drugs (5/0), including three iron compounds, two iron compounds, folic acid and vitamin B12; 4) other unspecified vitamins (4/0); 5) antiemetic drugs (5/4); 6) analgesics (0/7); 7) spasmolytics (0/5).

Twelve mothers of VATERL cases had been exposed to physical agents during pregnancy, vs. three mothers of malformed controls ($P < 0.03$). The physical agents mentioned in the VATERL group were X-rays (6/3), severe trauma (5/0 cases), and a retained intrauterine device (1/0 case).

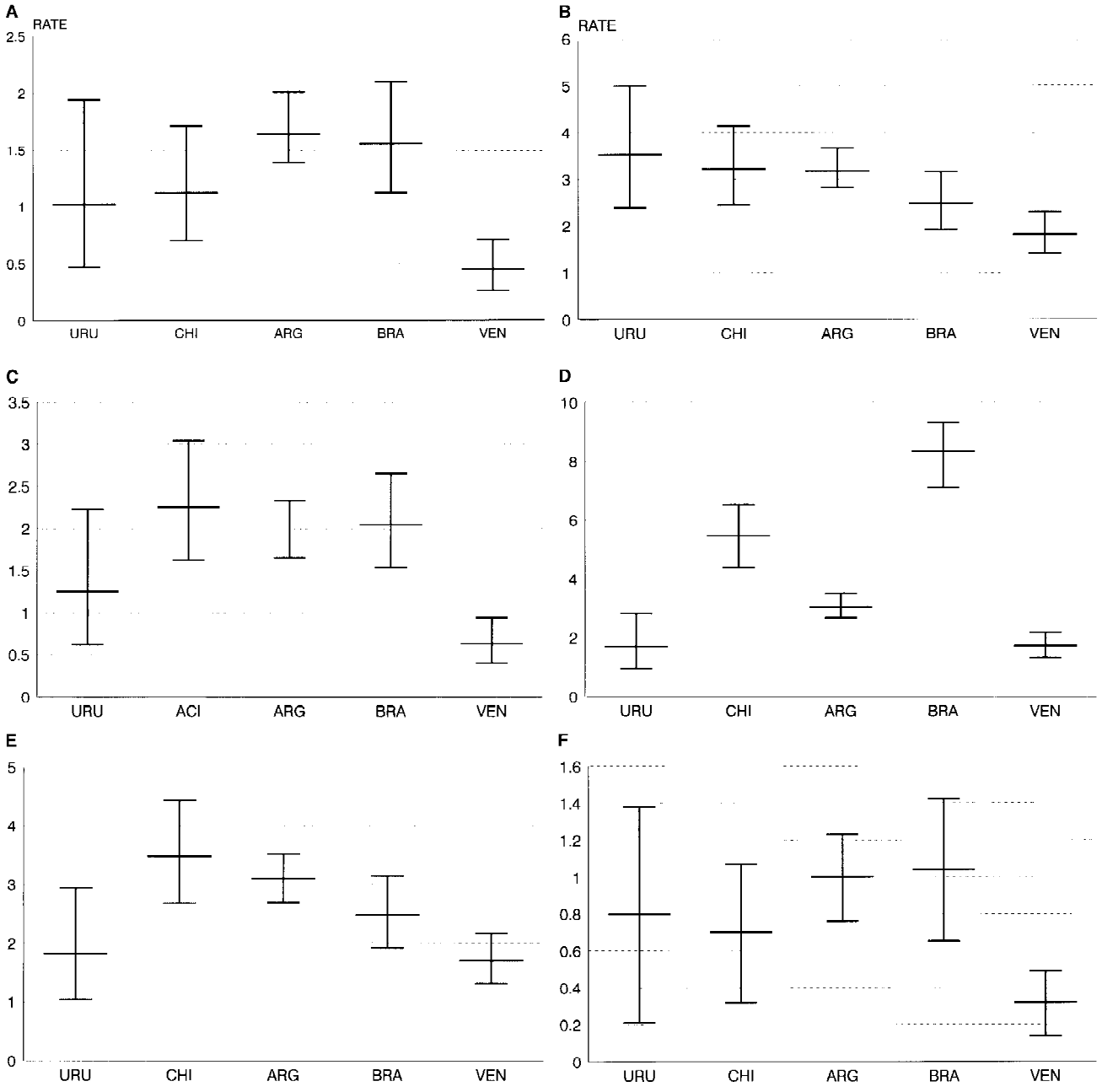
Affected Relatives

There was no statistically significant difference in the frequency of infants with one or more relatives affected by any congenital anomaly between VATERL cases (19.7%) and malformed controls (26.5%) ($P = 0.242$) (Table V).

Seven of the 26 VATERL cases with a positive family history had one affected first-degree relative, and 2 had two of them (mother and brother; mother and like-sexed twin). Five (1.8%) of 276 VATERL cases' parents had a congenital anomaly, none of them being a VATERL component. Six (2.1%) of 292 VATERL cases' sibs were affected, including 4 twins of the same sex and unknown zygosity. Three of those twins had one or more VATERL component anomalies also present in the index case (Table VI).

One of the remaining 17 VATERL cases with a family history for congenital anomalies was an index case with VL, who had a grand-aunt, a sister of the maternal grandfather, with a vertebral defect (V), and a cousin once removed with postaxial polydactyly.

Among 138 malformed controls, 36 (26.5%) had one



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	Vertebral	Anal	TE	Renal	Limb	VATERL
Uru	0.47-1.02-1.94	2.39-3.52-4.99	0.62-1.25-2.23	0.95-1.7-2.81	1.04-1.82-2.95	0.21-0.80-1.38
Chi	0.7-1.12-1.71	2.45-3.21-4.13	1.62-2.25-3.04	4.39-5.46-6.53	2.68-3.48-4.43	0.32-0.70-1.07
Arg	1.39-1.64-2.01	2.82-3.17-3.66	1.65-2.01-2.33	2.68-3.04-3.52	2.69-3.1-3.52	0.76-1.0-1.23
Bra	1.12-1.55-2.1	1.92-2.48-3.15	1.53-2.04-2.65	7.11-8.33-9.33	1.92-2.48-3.15	0.65-1.04-1.42
Ven	0.26-0.45-0.71	1.41-1.81-2.29	0.4-0.63-0.94	1.34-1.73-2.2	1.32-1.7-2.17	0.14-0.32-0.49

Fig. 1. Geographical distribution of the prevalence rates per 10,000 births (with 0.05 CI) for each of the five component anomalies of the VATERL association in non-VATERL cases, and in 138 cases presenting two or more VATERL component anomalies. **A:** Vertebral anomalies. **B:** Anal atresia. **C:** Esophageal atresia. **D:** Renal anomalies. **E:** Preaxial upper limb anomalies. **F:** VATERL cases. **G:** Points of the six components (95% confidence lower limit–rate–95% upper confidence limit).

TABLE V. Case-Control Analysis in 138 VATERL Cases and Matched Controls*

Variable	VATERL cases N	%	T	Controls N	%	P
Twinning	6/137 (1)	4.4	H	2/138	1.5	0.139
Mortality	86/135 (3)	63.7	H	0/137 (1)	0.0	0.001
Primigravida	46/137 (1)	31.4	H	37/138	26.8	0.275
Consanguinity	2/124 (14)	1.6	H	1/136 (2)	0.7	0.465
Black ancestry	7/120 (18)	5.8	H	14/128 (10)	10.9	0.224
Native ancestry	54/120 (18)	45.0	H	53/128 (10)	41.4	0.658
Low mat education	35/126 (12)	27.8	H	46/134 (4)	34.3	0.314
Low pat education	32/118 (20)	27.1	H	37/131 (7)	28.2	0.955
Low mat occupation	73/91 (47)	80.2	H	87/98 (40)	88.8	0.153
Low pat occupation	28/121 (17)	23.1	H	35/132 (6)	26.5	0.635
Subfertility	15/125 (13)	12.0	H	9/136 (2)	6.6	0.197
Previous miscarriages						
All pregnancies	54/428 (1)	12.6	H	34/439	7.7	0.024
Preceding pregnancy	21/90	23.3	H	14/101	13.9	0.08
Gestation age						
N	75 (63)		H	99		
M	37.7			39.5		
SD	4.4			2.2	0.001	
Birthweight						
N	137 (1)		H	138		
M	2,361.79		3,259.20			
SD	809.63			495.04		0.001
Maternal age						
N	138		H	138		
M	26.44			26.02		
SD	6.75			7.06		0.620
Paternal age						
N	126 (12)		H	136 (2)		
M	29.87			29.33		
SD	7.87			7.73		0.593
Malformed relative	26/132 (6)	19.7	M	36/136 (2)	26.5	0.242
FT acute illness	23/126 (12)	18.3	M	14/134 (4)	10.5	0.105
FT chronic illness	18/126 (12)	14.3	M	15/135 (3)	11.1	0.559
FT immunization	4/126 (12)	3.2	M	2/134 (4)	1.5	0.369
FT drugs	54/127 (11)	42.5	M	37/134 (4)	27.6	0.017
FT vaginal bleeding	21/127 (11)	16.5	M	16/133 (5)	12.0	0.389
FT physical agents	12/124 (14)	9.7	M	3/132 (6)	2.3	0.024

*T, type of control; H, healthy; M, malformed ( ) number of cases with missing data; mat, maternal; pat, paternal; FT, first trimester of pregnancy.

or more malformed relatives (two cases unspecified). Eleven (4.8%) of 227 sibs and 6 (2.2%) of 276 parents had a congenital anomaly. Only one malformed control had a VATERL component, an isolated vertebral defect. His like-sexed twin of unknown zygosity had anal atresia and a vertebral defect.

TABLE VI. Congenital Anomaly Types in 11 Affected First-Degree Relatives of Nine VATERL Propositа

Propositus N	Propositus Defects	Relative Kin	Relative Defects
1	ATE	Twin	ATE
2	ALV	Twin	ALV
3	AV	Twin	V
4	AR	Sister	Heart defect
5	ARV	Father	Amputation of toes on both feet
6	TEV	Mother	Pulmonary valvular stenosis
7	AL	Mother	Supernumerary nipple
8	TEV	Twin	Congenital dislocation of the hip
		Mother	Microtia, left side
9	AR	Brother	Postaxial polydactyly
		Mother	Postaxial polydactyly

DISCUSSION

Due to differences in defining the VATERL association, it is difficult to compare the observations made in a given series of cases with those published by other authors. The material included here considered cases with two or more of five cardinal anomalies (V, A, TE, R, L), not including heart defects, accepting only radial defects as the limb component, and having no other unrelated anomalies described in the same infant. This working definition, based on a previously published association analysis [Rittler et al., 1996], is as unique as any of the other published definitions, and this fact must be borne in mind when observations are being compared. Among the three large epidemiological studies found in the literature, Khoury et al. [1983] defined VACTERL as three or more VACTERL anomalies, including heart defects, and any type of limb malformation or deformity, with or without other unrelated anomalies present; Czeizel and Ludányi [1985] considered three or more VACTERL anomalies, including heart defects and radial type of limb reduction defects or polydactyly, with no other unrelated anomalies pres-

ent; Botto et al. [1997] considered three or more VATERL anomalies, under definitions very similar to those used in the present work.

Secular Trends

The increasing secular trend of the observed birth prevalence rate of cases with the VATERL association seems to be secondary to the improvement in the perinatal ascertainment of most congenital anomalies [Castilla and Lopez-Camelo, 1990], since elective termination of pregnancy is not available in Latin America. In this aspect, the role of perinatal ultrasonography in the diagnosis of congenital anomalies seems to have been increasing, especially during the last 10 years. Thus, renal anomalies (R), the VATERL component with the lowest observational value, displayed the largest increase in secular trend. The great increase in the number of births during the period 1992–1994 should be due to the inclusion in this case-control study of hospitals which previously had been working under different conditions in epidemiologic surveillance of congenital malformations.

Low Frequency in Venezuela

The lower birth prevalence rate of VATERL in the Venezuelan subsample seems to be real. The large statistically significant difference between Venezuela and the remaining eight South American countries precludes random variation. On the other hand, the homogeneity between the two regions of Venezuela (east and west) into which the six observational units (maternity hospitals) were grouped, as well as the observed birth prevalence rate for VATERL cases in neighboring Colombia being higher than that of Venezuela and similar to the rest of South America, indicates that this low frequency is exclusive to Venezuela in our material. Furthermore, the above-mentioned geographic differences for VATERL as well as for each of the five congenital anomalies involved in this association provides a strong biological meaning to this finding.

The lower birth prevalence rate for esophageal atresia in Venezuela was already recognized in a previous publication with ECLAMC material [Robert et al., 1993]. Furthermore, Orioli and Grisolia [1992] reported geographical heterogeneity for two of the five VATERL components, namely, renal anomalies (agenesis and cystic kidneys) and esophageal atresia, among other non-VATERL defects, but not for anal atresia, nor for preaxial limb defects; vertebral defects were not included in their study. These differences between their results and those presented here could be due to the different time intervals used in both investigations.

In South America, the different frequencies of some congenital anomalies among countries could mostly be due to different ethnic proportions in the complex racial admixture of our populations [Lopez-Camelo and Orioli, 1996]. However, to the authors' knowledge, there is no evidence in the literature for a racial uniqueness for Venezuela when compared with the other South American countries. Furthermore, the trihybrid admixture involving Latin-Europeans, Amerindians, and African blacks, which, in varying proportions is common to most of the South American population, is expected to vary also between different geographic regions and different social classes in Venezuela. Nevertheless, the six Venezuelan hospitals participating in our study share similarly low frequencies of the VATERL association and its component anomalies, in spite of sampling out different population subsets: namely, in the first place, the six hospitals mentioned belong to two different health systems, four are public and two private, serving different socioeconomic strata. In the second place, they are located in six different cities (Caracas, Ciudad Bolivar, Coro, Maracaibo, Cabimas, Ciudad Ojeda) of four states (Federal District [FD], Oriente, Falcon, Zulia) comprising four different geographic regions, namely, FD, Guyana, Coast, and Northwest, respectively [Castilla et al., 1995].

Since we failed to find a potential risk factor, either genetic or environmental, which could explain the low birth prevalence rate of VATERL in Venezuela, or a common cause of underascertainment, unique to the Venezuelan subsample and common to all 6 observational units, no hypothesis is advanced here for this phenomenon. Nevertheless, this geographically unequal distribution strongly suggests a common etiopathogenicity for the 5 congenital anomalies involved in the VATERL association.

We could not find any other publications concerning the geographical distribution of VATERL, which seems to have no ethnic preferences. However, an international study found lower than expected birth prevalence rates for esophageal atresia in Mexico and Norway [Robert et al., 1993].

Sex, Mortality, Birthweight

The observed predominance of male sex has already been mentioned for isolated VATERL by Czeizel and Ludányi [1985] only, and for both isolated and associated VATERL cases by Khoury et al. [1983].

The high perinatal mortality (63.7%) was mainly due to early neonatal death (49.6%) and to a lower extent to fetal death (14.1%), which could indicate that survival in VATERL mainly depends on the severity of the malformations present in each case. In our populations, the frequencies of fetal losses and of early neonatal mortality are approximately equal (2% of all births each); thus, in VATERL there is a 7-fold increase for fetal and a 25-fold increase for early neonatal deaths. As our material only includes infants with a birthweight greater than 500 g, early fetal and embryonic losses are obviously excluded from our study.

The observations that one half of the VATERL cases were preterm pregnancies and that birthweights were low at any gestational age differ from that of Czeizel and Ludányi [1985], who reported a higher frequency of preterm infants in VATERL and a lower birthweight in full-term than in preterm infants.

The higher mortality in VATERL cases born before 35 weeks of gestation could entirely be due to prematurity, but also to the renal anomalies (R component)

producing both premature birth and higher mortality through oligohydramnios. Sixteen of the 28 premature cases had R, and 15 of them died perinatally. Among the other 12 cases without an R component, 3 survived the first week of life. Even though the small number of cases precludes a conclusion, this observation could suggest that the subset of VATERL cases involving R anomalies tends to be premature, with a high mortality rate.

The higher rate of miscarriages in previous pregnancies in the VATERL group, already mentioned by Czeizel and Ludányi [1985], could reflect a genetic background, expressing itself through pregnancy losses or through congenital anomalies.

Prenatal Exposures

The available information on prenatal exposures to maternal illness, drugs, radiations or other physical agents, pregnancy complications, and low socioeconomic levels, did not show any significant association with VATERL. Nora and Nora [1973] suggested an association between prenatal exposure to exogenous sex hormones during the first trimester of pregnancy and the occurrence of VATERL. This could not be supported by a case-control study published by Lammer et al. [1986], nor by our data which registered exposure to sex hormones in 9 of 138 VATERL cases (6.5%), and in 6 of 138 malformed controls (4.4%).

Family History

No differences were found between cases and controls for family history data, including racial extraction, parental consanguinity, parental ages, and affected relatives. The literature mentions a low recurrence risk for VATERL as a whole [Czeizel and Ludányi, 1985; Evans et al., 1985; Czeizel et al., 1994]. However, when its individual components are considered, the recurrence risk in offspring or sibs of an affected individual could be considerably higher. According to McMullen et al. [1996], there also seems to be an increased risk of individuals with TE to exhibit other VATERL malformations and one half of their 140 cases with esophageal atresia would fit our definition of VATERL association. From their study, these authors concluded that the recurrence risk for affected individuals to have first-degree relatives with TE is around 2%. Though isolated TE is thought to be a multifactorial trait, a single gene could be responsible in some families [Pletcher et al., 1991; Warren et al., 1979]. King et al. [1977] described monozygotic female twins, both with TE and one with additional vertebral anomalies, anal atresia, and genital and renal anomalies. Auchterlonie and White [1982] described two sibs, one with TE and hemivertebrae and the other with TE, bilateral renal agenesis, anal atresia, and a ventricular septal defect. In our material, the recurrence for one or more VATERL components in first-degree relatives was limited to three like-sexed twin pairs, supporting the frequently mentioned hypothesis [Lubinsky, 1994] that genetic factors seem to play a very small role in the etiology of the VATERL association.

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